COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN

Patent Number:	WO9501183
Publication date:	1995-01-12
Inventor(s):	HARRIS ALAN
Applicant(s)::	FERRING AB (SE)
Requested Patent:	WO9501183
Application Number:	WO1994SE00623 19940622
Priority Number (s):	US19930084894 19930629
IPC Classification:	A61K37/34
EC Classification:	A61K9/00M14, A61K38/11
Equivalents:	CA2166312, CN1126439, CZ9503390, EP0708657 (WO9501183), HU73776, JP9502425T, NZ268442, PL312204, RU2135204, SK165095

Abstract

An aqueous composition for spray nasal administration of a synthetic analog of vasopressin (desmopressin; 1-deamino-8-D-arginine-vasopressin) contains between 2.5 and 7.5 mu g per 100 mu l. The composition may additionally contain an osmotic-pressure controlling agent, such as sodium chloride, a preservative, such as chlorobutanol or benzalkonium chloride, and a buffer stabilizing the pH between about 4 and 6. Buffers containing citrate and/or phosphate are preferred. Also disclosed is a sealed container filled with the composition, an assembly comprising the container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 37/34

A1

(11) International Publication Number: WO 95/01183

(43) International Publication Date: 12 January 1995 (12.01.95)

(21) International Application Number: PCT/SE94/00623

(22) International Filing Date: 22 June 1994 (22.06.94)

(30) Priority Data:
084,894 29 June 1993 (29.06.93) US

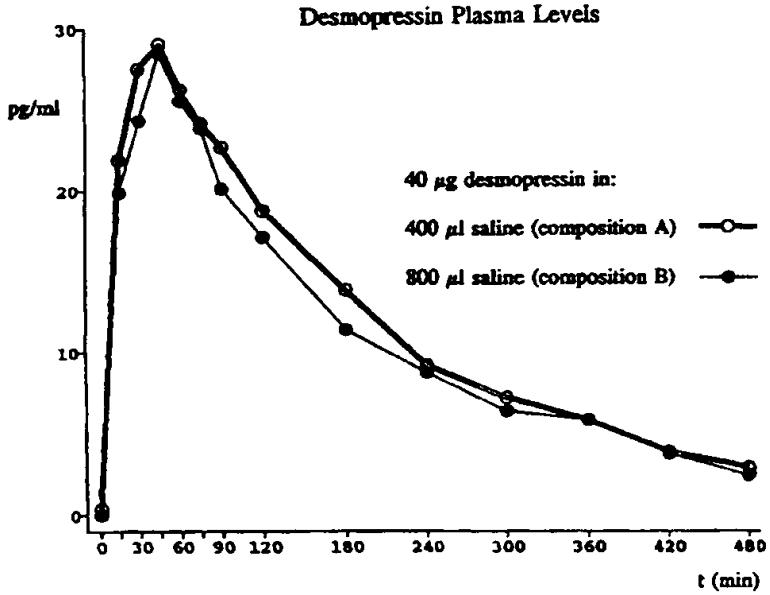
(71) Applicant: FERRING AB [SE/SE]; P.O. Box 30047, S-200 61 Malmö (SE).

(72) Inventor: HARRIS, Alan; Sövdeborgsgatan 4, S-216 19 Malmö (SE).

(81) Designated States: BG, BR, BY, CA, CN, CZ, FI, HU, JP, KR, LV, NO, NZ, PL, RO, RU, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN



(57) Abstract

An aqueous composition for spray nasal administration of a synthetic analog of vasopressin (desmopressin; 1-deamino-8-D-arginine-vasopressin) contains between 2.5 and 7.5 µg per 100 µl. The composition may additionally contain an osmotic-pressure controlling agent, such as sodium chloride, a preservative, such as chlorobutanol or benzalkonium chloride, and a buffer stabilizing the pH between about 4 and 6. Buffers containing citrate and/or phosphate are preferred. Also disclosed is a sealed container filled with the composition, an assembly comprising the container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

COMPOSITIONS FOR NASAL ADMINISTRATION OF DESMOPRESSIN.

The present invention is a composition for spray delivery to the nasal mucosa of 1-deamino-8-D-arginine-vasopressin (desmopressin).

Desmopressin, 1-(3-mercaptopropionic acid)-8-D-arginine-vasopressin (hereinafter also abbreviated as "DDAVP") is an analog of the neurohypophyseal peptide vasopressin. DDAVP is indicated in the management of a variety of medical conditions such as irregular urination or diurea, particularly those associated with diabetes insipidus and nocturnal enuresis.

DDAVP is currently available as an aqueous nasal spray composition which is administered by means of a metered spray pump. For instance, MINIRIN® nasal spray, Ferring AB, Sweden, contains 10 μg of desmopressin acetate per 100 μl, 0.5 % of chlorobutanol (w/v) as preservative, and sodium chloride. Intranasal administration of about 200 μl MINIRIN® spray, containing about 20 μg of desmopressin, provides an antidiuretic effect lasting in most adult patients for about 8 to 12 hours.

In a minority of cases a dose of up to 40 μg (400 μl) is required for similar effects.

For most nasally administered agents, the capacity of the human nasal cavity surface for holding aqueous solutions is limited. In most adults, this capacity is about 400 μl. For efficient systemic absorption of nasally administered therapeutics, the vehicle carrying the drug must remain in contact with the mucus-lined epithelium for a sufficient period of time.

400 μl volume is close to the maximum useful volume for known nasal spray compositions containing desmopressin. Nasal spray compositions having low concentrations of

DDAVP might allow coverage of a wider range of patients, such as including very young or elderly patients. However, even such dilute concentrations must be delivered in minute doses because of the potency of DDAVP. On the other hand, about 100 µl (containing a dose of 10 µg) of known solutions containing DDAVP is the lowest dose volume that can be conveniently reproduced by single actuations of the metered spray pump, and remain therapeutically effective.

Harris et al., J. Pharm. Sci. 77 (1988) 337-339, conducting experiments based on healthy human volunteers, state that a given amount of desmopressin in larger volume, when given in a single dose, is absorbed substantially less effectively than the same amount in a smaller volume (see Fig. 1, Harris, ibid.). These findings are in full agreement with those of Anik et al., J. Pharm. Sci. 73 (1984) 684-685, who conducted similar tests on rhesus monkeys with nasally administered solutions containing the decapeptide nafarelin acetate. Both reports favor higher concentrations and discourage use of more dilute solutions.

The known results obtained with desmopressin are based on analysis of plasma levels of desmopressin and factor VIII:C. The release into plasma of factor VIII:C is known to be stimulated by high doses of desmopressin. The dosage administered intranasally in such experiments was approximately 300 µg, about ten times the average dose given to patients with urinary disorders.

Thus, there exists a problem in the art for achieving a balance between therapeutic needs and dosage related problems of DDAVP nasal compositions. There is a need in the art for precisely metered, easily administered, and consistently reproducible nasal delivery compositions containing DDAVP.

An object of the present invention is to provide a nasal spray composition containing desmopressin which allows effective delivery to a wider range of patients, including very young and elderly patients.

Another object is to provide an aqueous composition for nasal administration of between 2.5 and 7.5 μg of desmopressin per 100 μl, which allows consistent delivery of optimum therapeutic doses of the DDAVP.

Further objects include the provision of a sealed container for delivery of DDAVP nasal compositions, an assembly comprising the sealed container and a spray pump, and the use of the composition, the container, and the assembly in the management of urinary disorders.

It has now been surprisingly found that the known relationship between the concentration of desmopressin in the aqueous carrier for nasal spray administration, said concentration being a desmopressin concentration of at least 1 μg per 100 μl, and desmopressin uptake by the nasal mucosa, which relationship dissuades from using more dilute solutions, does not hold for substantially smaller desmopressin concentrations, such as concentrations ranging from 2.5 μg to 7.5 μg per 100 μl.

In accordance with the invention, there is disclosed an aqueous nasal spray composition containing between 2.5 and 7.5 μg of desmopressin per 100 μl, the preferred concentration being about 5 μg desmopressin per 100 μl aqueous composition. It has been unexpectedly found that these optimum ranges provide ideal nasal delivery conditions for optimal therapeutic effects for desmopressin.

A preferred embodiment of the composition according to the present invention comprises an osmotic pressure-

controlling agent, such as sodium chloride, and a preservative, such as chlorobutanol or a quaternary amine preservative such as benzalkonium chloride.

According to another embodiment, the composition additionally comprises a buffer, preferably a buffer comprising citrate and/or phosphate. The buffer used in the present compositions should maintain the pH from about 4 to about 6, preferably a pH of about 5.

It is especially preferred for the composition to comprise both benzalkonium chloride and the above-defined buffer, which makes the DDAVP nasal compositions of the present invention room-temperature stable, with shelf lives exceeding one year.

Additionally the composition according to the invention may contain absorption enhancers such as bile salts, monolauryl ethers of macrogols, phospholipids and fusidate derivatives.

It is preferred for the composition according to the invention to be administrable in a metered dose or multiples thereof, said metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved in from 50 μl to 150 μl of an aqueous carrier to provide a desmopressin concentration in said carrier ranging from 2.5 μg to 7.5 μg per 100 μl, for effecting a plasma profile essentially corresponding to that obtainable by single or multiple dose nasal administration of the same total amount of desmopressin dissolved in said carrier in substantially higher concentration.

It is also preferred for the composition according to the invention to be administrable in a metered dose or multiples thereof, said metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved in from 50 μl to

150 µl of an aqueous carrier, for effecting a plasma profile essentially equivalent, on a desmopressin unit dose weight basis, to a desmopressin plasma profile obtainable by nasal administration of a metered dose of desmopressin comprising substantially higher amounts of desmopressin in a corresponding smaller volume of aqueous carrier ranging from 50 µl to 150 µl.

Also disclosed is a sealed container filled with an aqueous desmopressin spray composition according to the invention and its use in connection with a spray pump. The container and the pump may be integrated as a unit and can also be made disposable. It is preferred for the pump to be a metered precompression spray pump. The pump is preferably designed for delivering a dose ranging from 2.5 to 7.5 µg desmopressin per actuation, with the optimum amount at about 5 µg.

The composition according to the invention is used for effective therapeutic management of various urinary disorders, such as diabetes insipidus, incontinence, and enuresis, particularly nocturnal enuresis.

FIGURE 1 graphically depicts therapeutical bioequivalence of known DDAVP nasal solutions and the DDAVP aqueous nasal compositions of the present invention.

The invention will now be explained in detail by reference to the following experimental examples.

EXAMPLE 1

Preparation of test solutions. Two desmopressin acetate nasal spray compositions (A and B) were prepared under aseptic conditions by dissolving the following components in 1 l of Millipore®-filtered water:

composition	A	B
desmopressin acetate	100 mg	50 mg
chlorobutanol*	5 g	5 g
sodium chloride	9 g	9 g

* 1,1,1-trichloro-2-methylpropan-2-ol

pH was adjusted to 3.5 - 5.0 by addition of 2 N HCl. A denotes a currently known composition which was prepared for comparison, while B denotes the composition made according to the present invention.

EXAMPLE 2

Comparative testing. 24 healthy male volunteers were given 40 μg of desmopressin in the form of composition A from Example 1 (administration of a 4 x 100 μl = 400 μl dose). After an interval of at least one week, the same test subjects were given desmopressin in the form of composition B (administration of a 8 x 100 μl = 800 μl dose). Commercially available, metered-dose spray pumps manufactured by Erich Pfeiffer AG, Rudolfzell, Germany, set to the appropriate dosage volumes were used.

Blood was collected by venipuncture before administration (control) and at times 5, 15, 30, 45, 60, and 90 minutes, and 2, 4, 6, and 8 hours after administration. Plasma desmopressin was assayed by RIA as described by Harris, et al., J. Pharm. Sci. **77** (1988) 337-338 (for statistical treatment of data, see Harris ibid., p. 338).

The results are graphically depicted in Fig. 1, which shows plasma levels of desmopressin as a function of time. It is evident from Fig. 1 that composition (A) and the composition according to the present invention (B) are bioequivalent and therefore therapeutically equivalent. It

can also be seen that composition (B) has a substantially broader useful administration range.

EXAMPLE 3

Long shelf-life composition. A nasal spray composition according to the present invention having a shelf life of more than one year at room temperature was prepared by dissolving in 1000 ml of Millipore®-filtered water: 50 mg of desmopressin acetate, 1.0 g of benzalkonium chloride, 6.3 g of sodium chloride, 1.56 g of citric acid, and 2.43 g of disodium hydrogen phosphate.

While the various embodiments of the present invention have been described herein, it is possible that one skilled in the art could modify the various reagents and reaction conditions and obtain similar results. Such modifications are contemplated as being within the scope of the present disclosure.

Claims

1. An aqueous composition for nasal administration of desmopressin, comprising between about 2.5 and about 7.5 μg desmopressin per 100 μl of said aqueous composition.

2. The composition according to claim 1, wherein said composition contains about 5 μg desmopressin per 100 μl.

3. The composition according to claim 1, further comprising an osmotic pressure-controlling agent.

4. The composition according to claim 3, wherein said osmotic pressure-controlling agent is sodium chloride.

5. The composition according to claim 1, further comprising a preservative.

6. The composition according to claim 5, wherein said preservative is chlorobutanol.

7. The composition according to claim 5, wherein said preservative is a quaternary amine.

8. The composition according to claim 7, wherein said quaternary amine is benzalkonium chloride.

9. The composition according to claim 1, further comprising a buffer.

10. The composition according to claim 9, wherein said buffer comprises citrate and/or phosphate.

11. The composition according to claim 10, wherein said buffer maintains a pH from about 4 to about 6.

12. The composition according to claim 11, wherein said buffer maintains pH at about 5.

13. The composition according to claim 1, further comprising at least one absorption enhancing agent.

14. The composition of claim 13, wherein said absorption enhancing agent is selected from the group consisting of bile salts, monolauryl ethers of macrogols, phospholipids, and fusidate derivatives.

15. The composition according to rlaim 1, administrable in a metered dose or muitiples thereof, said metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved in from 50 μl to 150 μl of an aqueous carrier to provide a desmopressin concentration in said carrier ranging from 2.5 μg to 7.5 μg per 100 μl, for effecting a plasma profile essentially corresponding to that obtainable by nasal administration of the same total amount of desmopressin dissolved in said carrier in substantially higher concentration.

16. The composition according to claim 1, administrable in a metered dose comprising from 2.5 μg to 7.5 μg of desmopressin dissolved in from 50 μl to 150 μl of an aqueous carrier, for effecting a plasma profile essentially equivalent, on a desmopressin unit dose weight basis, to a desmopressin plasma profile obtainable by nasal administration of a metered dose of desmopressin comprising substantially higher amounts of desmopressin in a corresponding smaller volume of aqueous carrier ranging from 50 μl to 150 μl.

17. An aqueous composition for nasal administration of desmopressin, comprising:

a) between about 2.5 and about 7.5 μg desmopressin per

100 µl;

b) benzalkonium chloride;

c) an absorption enhancing agent selected from the group consisting of bile salts, monolauryl ethers of macrogols, phospholipids, and fusidate derivatives; and

d) a buffer comprising phosphate and citrate, such that said buffer has substantial buffering capacity at a pH from 4 to 6.

18. A sealed container containing an aqueous desmopressin spray composition according to claim 16.

19. An assembly comprising a sealed container according to claim 18 and a precompression spray pump.

20. The assembly according to claim 19, wherein said spray pump delivers a dose volume containing from about 2.5 µg to about 7.5 µg desmopressin per actuation.

21. The assembly according to claim 20, wherein said dose volume contains about 5.0 µg desmopressin per actuation.

22. A method for treating urinary disorders with the composition according to claim 1.

23. The method of claim 22, wherein said disorder is selected from the group consisting of diabetes insipidus, incontinence, enuresis and nocturnal enuresis.

24. A method for treating urinary disorders with the composition according to claim 17.

25. The method of claim 24, wherein said disorder is selected from the group consisting of diabetes insipidus, incontinence, enuresis and nocturnal enuresis.

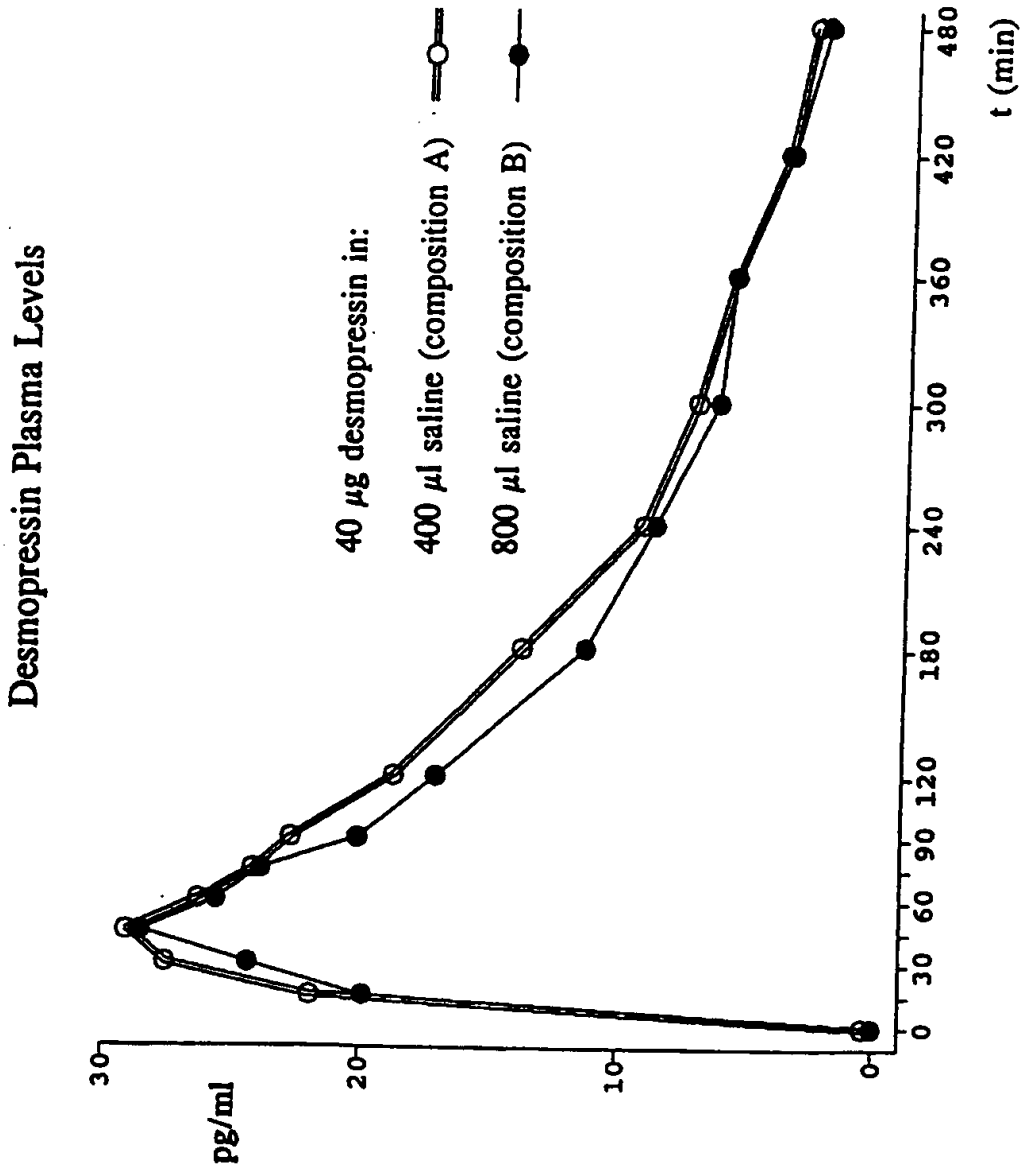

Desmopressin Plasma Levels
40 μg desmopressin in:
400 μl saline (composition A)
800 μl saline (composition B)
pg/ml
30
20
10
0
0
30
60
90
120
180
240
300
360
420
480
t (min)

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00623

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 37/34
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, BIOSIS, EMBASE, WPI, CLAIMS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0381345 (CORINT, LTD.), 8 August 1990 (08.08.90) --	1-21
A	WO, A1, 8805661 (BIOMED RESEARCH CONSULTANTS LIMITED), 11 August 1988 (11.08.88) --	1-21
A	The Lancet, 1968, I Vavra et al: "Effect of a Synthetic Analogue of Vasopressin in Animals and in Patients with Diabetes Insipidus", see page 948 - page 952 --	1-21

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"B" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 1994	12 -10- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Elisabeth Carlborg Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00623

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 22-25
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

27/08/94

International application No.
PCT/SE 94/00623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0381345	08/08/90	AT-T- 108326	15/07/94
		DE-D- 69010518	00/00/00
WO-A1- 8805661	11/08/88	EP-A- 0300036	25/01/89